Comparison of ICD shock rates in Japanese and non-Japanese patients in the PainFree SST study

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Abstract: BACKGROUND The PainFree Smart Shock Technology (SST) study showed a low implantable cardioverter-defibrillator (ICD) inappropriate shock rate. However, the majority of patients were from Western countries with patient characteristics different from those in Japan. ICD shock rates using the novel SST algorithms in Japanese patients are still unknown. METHODS All 2,770 patients in the PainFree SST study (Japan [JPN]: N = 181, other geographies [OJPN]: N = 2,589) were included in this analysis. RESULTS Japanese patients had higher average left ventricular ejection fraction ($P < 0.0001$), higher prevalence of secondary prevention indications ($P < 0.0001$), nonischemic cardiomyopathy ($P < 0.0001$), and permanent atrial fibrillation ($P < 0.0001$). The appropriate shock rate at 12 months was not different between JPN and OJPN: 6.4% and 6.3%, respectively ($P = 0.95$). The inappropriate shock rate at 12 months was significantly higher in Japanese patients (2.9% vs 1.7%, $P = 0.017$). However, after propensity score matching to adjust for the difference in baseline characteristics, the difference in inappropriate shock rate was not statistically significant ($P = 0.51$). CONCLUSIONS There was no difference in the appropriate shock rate between Japan and other geographies. The inappropriate shock rate in Japan was low, although it was slightly higher compared to other geographies due to baseline characteristics, including a higher prevalence of permanent AF. There was not a statistically significant difference after adjusting for baseline characteristics.

DOI: https://doi.org/10.1111/pace.13427

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Short title: Comparison of ICD Shock Rates.

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Acknowledgement of grant support:
The PainFree SST study was funded by Medtronic, Inc.

Any potential conflicts of interest:
T Kurita received speaker fees from Medtronic, Biotronik, Boston Scientific, and St. Jude Medical. K Ando received a speaker fee from Medtronic. S Shizuta received speaker fees and research supports from Medtronic, St. Jude Medical, Boston Scientific, and Biotronik, and speaker fee from Japan Lifeline. H Okamura received scholarship funding from Medtronic. N Matsumoto received speaker fees from Bayer and Daiichi-Sankyo, and scholarship funding from Pfizer and Bristol-Myers Squibb. B Gerritse and D Fagan are employees and share owners of Medtronic. E Schloss received consultant

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pace.13427.

fees from Medtronic and Boston Scientific, and has Equity Interests/Stock Options in AliveCor. A Auricchio is a consultant for and received speaker fees from Abbott, Biosense Webster, BMS, Boston Scientific, Cardiotek-Schwarzer, Cordis Biologics Delivery Systems, DC Devices, Leadexx, Medtronic, Resmed, Respicardia, Schiller AG, Sorin Group, and St. Jude Medical. L Sterns received speaker fees from Boehringer Ingelheim, Pfizer, Bayer, and BMS. K Okumura received speaker fees from Medtronic, Daiichi-Sankyo, Bayer, Boehringer-Ingelheim and Johnson & Johnson.

Abstract (250 words)

Background: The PainFree Smart Shock Technology (SST) study showed a low ICD inappropriate shock rate. However, the majority of patients were from Western countries with patient characteristics different from those in Japan. ICD shock rates using the novel SST algorithms in Japanese patients are still unknown.

Methods: All 2,770 patients in the PainFree SST study (Japan [JPN]: N = 181, other geographies [OJPN]: N = 2,589) were included in this analysis.

Results: Japanese patients had higher average LVEF (P < 0.0001), higher prevalence of secondary prevention indications (P < 0.0001), non-ischemic cardiomyopathy (P < 0.0001), and permanent AF (P < 0.0001). The appropriate shock rate at 12 months was not different between JPN and OJPN: 6.4% and 6.3%, respectively (P = 0.95). The inappropriate shock rate at 12 months was significantly higher in Japanese patients (2.9% vs. 1.7%, P = 0.017). However, after propensity score matching to adjust for the difference in baseline characteristics, the difference in inappropriate shock rate was not statistically significant (P = 0.51).

Conclusions: There was no difference in the appropriate shock rate between Japan and other geographies. The inappropriate shock rate in Japan was low, although it was slightly higher compared to other geographies due to baseline characteristics including a higher prevalence of permanent AF. There was not a statistically significant difference after adjusting for baseline characteristics.

Key Words:

Implantable Cardioverter-Defibrillator; Cardiac Resynchronization Therapy; Heart Failure; Atrial Fibrillation; Inappropriate shock

Introduction:

A number of large-scale clinical studies have shown that implantable cardioverter-defibrillators (ICDs) are one of the most effective therapies to prevent sudden cardiac death regardless of the underlying cardiac condition (ischemic or non-ischemic) or the intended use (primary or secondary prevention).[1-3] Although appropriate ICD shocks improve survival, shocks may cause anxiety and psychological distress and increase mortality.[4-7] The PainFree SST clinical study was conducted to evaluate the efficacy of a novel suite of detection algorithms designated as "Smart Shock Technology". Use of this technology combined with modern programming led to a very low inappropriate shock rate in the range of 1.5% per year for dual-chamber ICDs.[8] Nevertheless, this clinical study was conducted mainly in Western countries and did not thoroughly reflect the patient background of the population from eastern Asia including Japan. It is known that patient baseline characteristics are different between Western countries and Japan.[9-10] However, it is unknown if these differences lead to different outcomes including the occurrence of inappropriate shocks. In this study, ICD shock rates from Japanese and non-Japanese patients who were enrolled in the PainFree SST study were compared to elucidate the effectiveness of the discrimination algorithms in the Japanese population. The impact of differences in patient baseline characteristics on inappropriate shock rates was assessed in order to inform ICD patient management.

Methods:

Study design:

The methods and primary results of the PainFree SST study have been published.[8] In brief, the study was a prospective, multi-center, global clinical study conducted mainly in the US,

Europe, Middle East, Asia, and Japan. The study enrolled patients who had a clinical indication for an ICD for either primary or secondary prevention of sudden cardiac death and intended to receive a single-chamber (SC) or dual/triple-chamber (DC) Protecta® device (Medtronic plc, Minneapolis, MN). The primary endpoint was the percentage of patients receiving at least 1 inappropriate shock at 12 months. Secondary endpoints included the percentage of patients receiving any inappropriate device therapy (i.e., shocks and/or anti-tachycardia pacing (ATP)) at 12 months, the causes of inappropriate shocks, the incidence of appropriate device therapy, and evaluation of any under- treatment of ventricular arrhythmias. All patients were followed until study closure but not less than 1 year. Total study duration was 4 years, from September 2009 until September 2013.

Device programming was mostly "out of box" settings. Ventricular Fibrillation (VF) detection zone was programmed with a detection interval of 320 ms. Ventricular Tachycardia (VT) detection zone was recommended to be programmed OFF in primary prevention patients and left to physician discretion in secondary prevention patients. Discrimination algorithms were programmed ON, per the nominal "out of box" settings of the device. Supra-ventricular tachycardia (SVT) discrimination algorithms were active for median ventricular intervals $\geq$ 260ms. In primary prevention patients, the VF number of intervals to detect (NID) was programmed to 30/40, which is clinically proven to safely reduce shocks.[11] Secondary prevention patients were randomized 1:1 to either VF NID 30/40 or 18/24.[12] Further details are described in the design paper.[13]

The PainFree SST study was approved by the local institutional review boards and informed consent was obtained from each patient prior to any study procedures taking

place. Episodes were adjudicated by an episode review committee comprised of 9 independent physicians who were not study investigators.

In this substudy, we compared subsets of PainFree SST study patients from Japan (JPN) and from other geographies (OJPN) to evaluate appropriate and inappropriate ICD shock rates in each group.

Statistical Methods:

Baseline characteristics and programming parameters are summarized using percentages for categorical variables and mean and standard deviation for continuous variables. Fisher exact test and t-test were used for frequency and continuous outcome, respectively, comparing JPN and OJPN patients.

The Kaplan-Meier method was used to estimate appropriate and inappropriate shock rates. Curves are presented with 95% log-scale confidence interval. The survival curves were compared for geographic subgroups (JPN vs. OJPN) with a log-rank test. Hazard ratios with their confidence interval were obtained from Cox regression. The interaction between geography and baseline variables was assessed by including separate baseline effects for JPN and OJPN patients. Given the broad inclusion criteria and regional differences in baseline patient characteristics, propensity score matching was applied to compare the inappropriate shock rate with adjusted baseline characteristics between the cohorts. Missing values of baseline characteristics were imputed first (multiple imputation). Propensity scores were calculated from a logistic regression model including the significantly different characteristics shown in Table 1 and averaged among the imputed data sets. Greedy matching was then implemented to find three OJPN patients to match one JPN

patient. Standardized differences were used to assess balance between JPN and matched OJPN patients, and a value ≤ 0.25 was considered acceptable balance.

Results:

Study population

In total, 2,770 patients consisting of 181 JPN patients (144 DC and 37 SC) and 2,589 OJPN patients (1,875 DC and 714 SC) were included in this study. The OJPN patients were predominantly from Western countries (United States 33.4%, Western Europe 32.9%, Southern Europe 11.1%, Canada 10.2%, Other 12.4%; Table S1 in the Online Appendix) and were largely of white/Caucasian race (80.9%). The follow-up durations of JPN and OJPN patients were 21 ± 6 months and 22 ± 10 months, respectively. There were many differences in baseline characteristics between the groups (Table 1). Notably, Japanese patients had a higher average left ventricular ejection fraction (LVEF, 44% vs. 31%, P < 0.0001), more received the ICD for secondary prevention (56% vs. 29%, P < 0.0001), fewer had ischemic cardiomyopathy (17% vs. 45%, P < 0.0001), more had permanent atrial fibrillation (AF, 19% vs. 9%, P < 0.0001), and more used antiarrhythmic drugs (40% vs. 17%, P < 0.0001). Permanent AF was present in 35.1% of Japanese patients implanted with SC ICDs (Table S2 in the Online Appendix). Propensity score matching successfully identified a sub-group of OJPN patients comparable to the JPN patients (Table 1), as demonstrated by standardized differences that were all less than 0.25, except for LVEF and Inotropic agent use (Figure S1 in the Online Appendix).

Device Programming

Although the majority of patients in this study were set to VF NID 30/40, a higher percentage of JPN patients were set to 18/24 than OJPN (28% vs 18%, P = 0.002) due to

randomization of the VF NID in secondary prevention patients. In addition, fewer JPN patients were programmed with Sinus Tachycardia Discrimination ON (86% vs. 98%, P < 0.0001). JPN patients were also programmed with a longer VF detection interval (307.8 ± 14.5 vs. 303.4 ± 17.5 ms, P = 0.0001), and a longer VT detection interval (393.2 ± 43.0 vs. 354.3 ± 30.0 ms, P < 0.0001) when VT detection was programmed ON (62% vs. 63%, P = 0.75).

Appropriate shock

There was no difference in the incidence of appropriate shocks in JPN compared to OJPN, both overall, and when stratified by indication (Figure 1, Online Appendix Figure S2). The appropriate shock rates at 12 months were 6.4% and 6.3% for JPN and OJPN, respectively (P = 0.95) (Figure 1). In addition, there was no difference in the incidence of appropriate shocks across other geographies (Online Appendix Figure S3).

Inappropriate shock

There was a higher incidence of inappropriate shocks in JPN compared to OJPN (at 12 months, 2.9% and 1.7%, respectively, P = 0.017, Hazard Ratio = 2.22) (Figure 2A). The incidence rate of inappropriate therapy (shock and ATP) after one year post-implant was 4.7% in JPN. Across OJPN geographies, the inappropriate shock rate was comparable except for a higher rate in Saudi Arabia (Online Appendix Figure S4).

In JPN patients, there was a difference in the inappropriate shock rate between patients with SC and DC devices (P=0.01) (Figure 2B); however, there was no difference in the inappropriate shock rate when comparing JPN and OJPN patients with DC devices (P = 0.21). Additionally, more JPN patients with inappropriate shocks had a history of permanent AF, compared to JPN patients without inappropriate shocks (P = 0.025) and OJPN patients

with inappropriate shocks (P = 0.006, Online Appendix Table S3). The most frequent adjudicated cause of an inappropriate shock for both JPN and OJPN patients was AF or atrial flutter (Table 2). The inappropriate shock rate was significantly higher for Japanese patients with permanent AF compared to OJPN patients with permanent AF (P = 0.004) but similar in patients without permanent AF (P = 0.52) (Figure 2C). After propensity matching to adjust for differences in baseline characteristics, there was no statistical difference in the inappropriate shock rate between JPN and OJPN (P = 0.51, Figure 3).

Discussion:

In a sub-analysis of JPN patients and OJPN patients from the PainFree SST study, we found the appropriate shock rate was comparable between groups. The inappropriate shock rate was higher in JPN than that of OJPN; however, after adjusting for differences in baseline characteristics, there was no longer a difference in the rate of inappropriate shocks. To our knowledge, this is the first report comparing the rates of appropriate and inappropriate shocks between JPN and OJPN using patients from a single study.

Appropriate shock rate

Although it was anticipated that the appropriate shock rate would be higher in the Japanese population since there were more patients receiving the device for secondary prevention,[14] results from this report showed that the incidence of appropriate shock was similar between JPN and OJPN (Figure 1). This may be related to the fact that the Japanese population in this study is comprised of patients with relatively good cardiac function, lower incidence of myocardial infarction, and fewer patients with ischemic cardiomyopathy, all of which have been reported to predict incidence of appropriate therapy (Online Appendix Figure S2).[15] Further research is warranted.

Inappropriate shock rate

Results from this sub-analysis of the PainFree SST study demonstrated that the inappropriate shock rate was significantly higher in Japanese patients. This could be explained by the difference in patient baseline characteristics as demonstrated by the propensity adjusted analysis. As seen in Table 1, many parameters are significantly different between JPN and OJPN, including the prevalence rates of Brugada syndrome and congenital long QT syndrome being significantly higher and the rate of ischemic cardiomyopathy being lower in JPN. It is noteworthy that prevalence of permanent AF, a well-known cause for inappropriate shocks, is high, especially in patients implanted with SC ICDs (35.1%). In Japan, SC ICDs are predominantly chosen for patients with permanent AF as atrial pacing and sensing are not necessary in this population. When SC ICDs are implanted in patients with permanent AF, advanced SVT discrimination algorithms such as PR logic® cannot be utilized; thus, the diagnosis must rely on the rate, stability criteria, and morphology, which may have less specificity and result in more inappropriate shocks.[8] In the present study, JPN patients only demonstrated a higher inappropriate shock rate in patients implanted with SC ICDs and not in those with DC ICDs. Additionally, since it has been reported that a ventricular rate above 90 - 110 bpm during AF increases the risk of inappropriate shock,[16-17] rate control during AF may also play a crucial role. In the ECOST trial,[18] the number of inappropriate shocks decreased by utilizing remote monitoring and diagnostic features of the ICD, facilitating early intervention to treat the conditions which may lead to inappropriate shocks. As such, rate control by utilizing remote monitoring could be an effective method to prevent inappropriate shocks.

Since secondary prevention use is the most common indication in Japan, the VT zone was programmed ON in many patients, with significantly longer detection interval than for OJPN, which may have increased the possibility of inappropriate shock. However, previous results from the PainFree SST study have shown that setting the VT zone ON did not affect the incidence rate of inappropriate shock. Additionally, the rate was similar among primary and secondary prevention patients.[8]

As differences in patient backgrounds between patients in JPN and OJPN may have contributed to the difference in inappropriate shock rate, a propensity analysis was performed. After propensity matching, the incidence rate of inappropriate shock was comparably low in JPN and OJPN. Ueda et al. have reported that the inappropriate shock rates in patients with a SC ICD or DC ICD were 19% or 12%, respectively, during 4.5 years of follow-up; however, the study excluded patients with a history of permanent AF.[19] Results from the largest-scale prospective registry study in Japan (Nippon Storm) have reported that the incidence rate of inappropriate therapy (shock and ATP) after one year post-implant was 6.7%,[19] which was higher than the 4.7% reported in this study. The registry period of Nippon Storm was almost the same as PainFree SST, and the patient backgrounds were similar; however, the implanted devices were different. Therefore, the difference in the incidence rate of inappropriate shock between these studies could support the effectiveness of Smart Shock Technology. The results of this study may help guide Japanese physicians in both the choice and programming of ICD devices. Furthermore, knowledge of regional differences in patient characteristics and current practice regarding device therapy makes it possible to develop ICD device algorithms and programming strategies that are tailored to the region.

Limitations:

Some limitations should be considered in interpreting the results of this study. The results were analyzed retrospectively and the number of Japanese patients was small. Study enrollment began later in Japan, thus the follow-up duration in Japanese patients is shorter; however, comparative results cover only the first 24 months post implant, which is within the Japanese patient follow-up duration. Propensity score matching analysis was conducted using only the baseline data collected in the PainFree SST study and does not take into account data not collected in the study that may impact the results. The matching reduced, but did not fully balance, the difference between Japanese and OJPN patients on LVEF and the use of inotropic agents.

Conclusion:

This is the first reported comparison of ICD shock rates between Japan and other geographies within the same study cohort. There was no difference in the appropriate shock rate between these two populations. The inappropriate shock rate in Japan was low, although it was slightly higher compared to other geographies, this was associated with differences in baseline characteristics including a higher prevalence of permanent AF and more use of single chamber ICDs in patients with permanent AF in Japan. The inappropriate shock rates were comparable between the geographies after adjusting for differences in baseline characteristics.

Acknowledgements:

The authors thank Medtronic employee Judith Raijmakers for study management.

ClinicalTrials.gov Identifier:

NCT00982397

Author contributions:

T. Kurita, Concept/design, Data collection, Data analysis/interpretation, Drafting article, Critical revision of article, Approval of article.

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S. Shizuta: Data collection, Critical revision of article, Approval of article

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Figure Legends

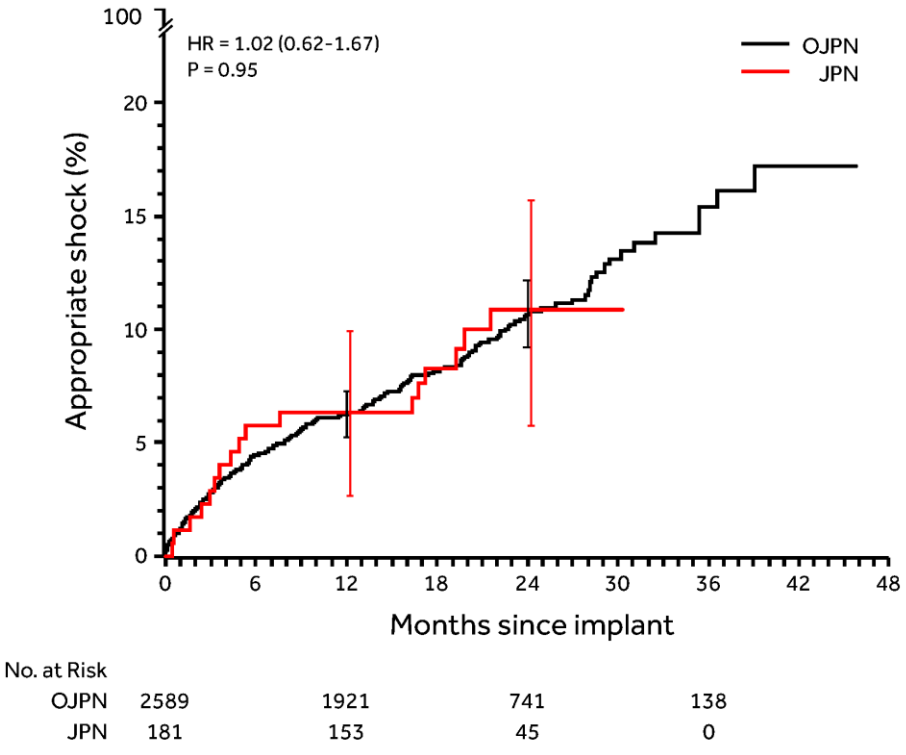

Figure 1. Appropriate shocks in Japan (JPN) and other geographies (OJPN). Follow-up duration is shorter in Japan as the study started earlier in Europe than Japan.

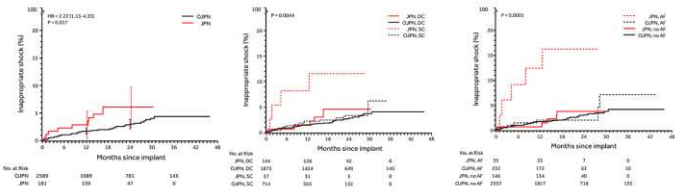

Figure 2A. Inappropriate shocks in Japan (JPN) and other geographies (OJPN).

Figure 2B. Inappropriate shocks by device type (single chamber (SC) and dual/triple chamber (DC)) in Japan (JPN) and other geographies (OJPN).

Figure 2C. Inappropriate shocks in patients with or without permanent atrial fibrillation (AF) in Japan (JPN) and other geographies (OJPN).

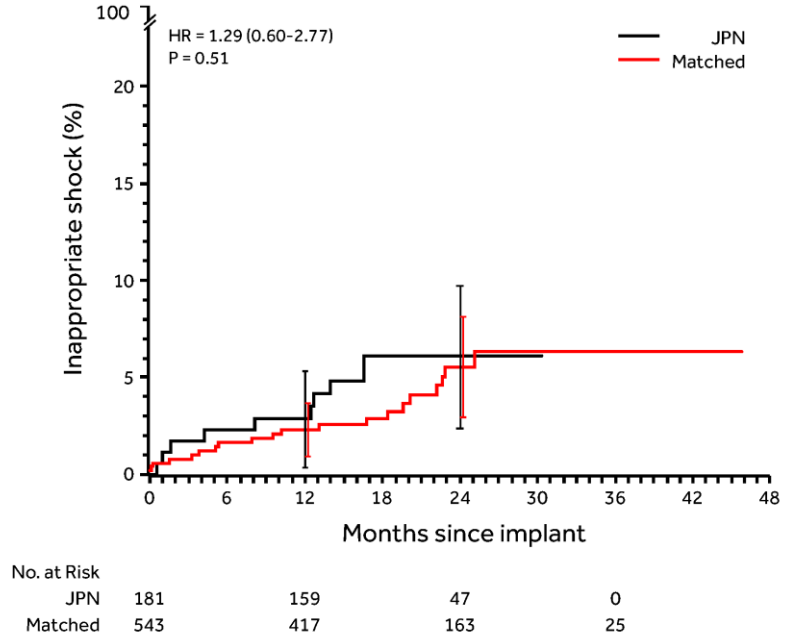

Figure 3. Inappropriate shocks in Japanese patients (JPN) and propensity-matched patients from other geographies (Matched).

Table 1. Baseline Characteristics

Patient Characteristics	Japan (N = 181)	Other geographies (N = 2,589)	Matched patients in Other geographies (N = 543)	P-value*
Gender, Male (%)	76.2	79.6	76.1	0.25
Age (years)	65.5 ± 12.1	64.8 ± 12.3	65.3 ± 13.3	0.49
LVEF (%)	43.9 ± 18.3	31.4 ± 12.3	38.2 ± 15.5	<0.0001
QRS (ms)	124.6 ± 33.9	126.0 ± 33.0	125.7 ± 33.4	0.58
Indication, Primary (%)	43.6	71.0	54.1%	<0.0001
NYHA class I/II/III/IV (%)	25/41/19/1	14/40/32/1	20/43/22/1	0.001
Brugada syndrome (%)	7.7	0.5	2.4	<0.0001
Cardiomyopathy, ischemic (%)	17.1	45.4	24.3	<0.0001
Congestive heart failure (%)	29.8	38.9	33.5	0.017
Coronary artery disease (%)	19.3	47.2	23.4	<0.0001
Hypertension (%)	26.0	54.0	35.0	<0.0001
Myocardial infarction (%)	17.1	39.3	24.5	<0.0001
Syncope, any (%)	32.6	14.4	22.1	<0.0001
Valve dysfunction, any (%)	14.4	25.9	16.8	<0.001
Coronary artery bypass graft (CABG) (%)	8.8	24.8	11.2	<0.0001
Previous device, any (%)	34.8	33.2	36.1	0.68
Atrial fibrillation (%)	38.1	28.9	33.9	0.011

Atrial fibrillation, paroxysmal (%)	11.0	14.7	14.7	0.19
Atrial fibrillation, persistent (%)	7.7	5.5	4.6	0.24
Atrial fibrillation, permanent (%)	19.3	9.0	14.7	<0.0001
Atrial flutter (%)	5.5	4.9	6.1	0.72
Atrial tachycardia (%)	3.3	2.0	2.6	0.27
Sinus bradycardia (%)	7.7	5.3	5.2	0.18
Long Q/T syndrome (%)	4.4	0.6	1.1	<0.0001
Ventricular fibrillation (%)	25.4	9.3	18.4	<0.0001
Ventricular tachycardia, any (%)	51.9	34.6	46.4	<0.0001
AV block, any (%)	17.1	14.4	14.5	0.33
Left bundle branch block (%)	13.3	26.1	19.2	<0.0001
Device detection (%)				0.038
Dual Chamber (ICD and CRT-D)	79.6	72.4	69.8	
Single Chamber	20.4	27.6	30.2	
Beta-Blocker (%)	69.1	86.7	77.2	<0.0001
ACE Inhibitor or ARB (%)	63.0	78.0	70.2	<0.0001
Diuretic (%)	58.6	68.8	64.3	0.006
Inotropic agent (%)	6.1	0.3	1.1	<0.0001
Calcium Channel Blocker (%)	18.8	10.5	16.0	0.001
Anti-Arrhythmic** (%)	40.3	17.2	32.6	<0.0001

*Japan vs. Other geographies, Student's t, Fisher exact and Cochran-Mantel-Haenszel testing.
** Predominantly Amiodarone or Sotalol.
ACE, Angiotensin converting enzyme; ARB, Angiotensin II receptor blocker; AV, atrio-ventricular; CRT-D, cardiac resynchronization therapy defibrillator; DC, dual chamber; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SC, single chamber.

Table 2. Cause of inappropriate shocks

Cause of inappropriate shock, patient (%, event)	Dual Chamber ICD/CRT-D		Single Chamber ICD	
	Japan (n = 144)	Other geographies (N = 1838)	Japan (N = 37)	Other geographies (N = 751)
Atrial fibrillation or atrial flutter	5 (3.4%, 7)	21 (1.1%, 34)	3 (8.1%, 3)	13 (1.7%, 22)
Other SVT	2 (1.4%, 2)	6 (0.3%, 9)	0	2 (0.3%, 2)
Committed shock after appropriate therapy	0	7 (0.4%, 7)	0	0
Ablation procedure	0	0	0	1 (0.1%, 1)
EGM noise	0	6 (0.3%, 21)	1 (2.7%, 1)	2 (0.3%, 2)
T-wave oversensing	0	4 (0.2%, 4)	0	0
Total	6 (4.2%, 9)	42 (2.3%, 75)	4 (10.8%, 4)	18 (2.4%, 27)

One inappropriate shock originally reported as due to other SVT was adjudicated again and the cause was changed to EGM noise after the publication of the primary results. SVT, supraventricular tachycardia; EGM, electrogram.